UNCLASSIFIED
SECURITY CLASSIFICATION OF THIS PAGE

(2)

REPORT DOCUMENTATION PAGE

AD-A211 160

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED	1b. RESTRICTIVE MARKINGS DTIC FILE COPY
2. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION / AVAILABILITY OF REPORT Approved for public release; distribution unlimited.
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) SR89-1[illegible]	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION Armed Forces Radiobiology Research Institute	6b. OFFICE SYMBOL (If applicable) AFRRI
7a. NAME OF MONITORING ORGANIZATION	
6c. ADDRESS (City, State, and ZIP Code) Bethesda, MD 20814-5145	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING / SPONSORING ORGANIZATION Defense Nuclear Agency	8b. OFFICE SYMBOL (If applicable) DNA
9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER	
8c. ADDRESS (City, State, and ZIP Code) Washington, DC 20305	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO.: NWED QAXM; PROJECT NO.: ; TASK NO.: ; WORK UNIT ACCESSION NO.: 00107
11. TITLE (Include Security Classification) (see reprint)	
12. PERSONAL AUTHOR(S) Gunter-Smith, P. J.	
13a. TYPE OF REPORT Reprint	13b. TIME COVERED FROM _____ TO _____
14. DATE OF REPORT (Year, Month, Day) 1989	15. PAGE COUNT [illegible]
16. SUPPLEMENTARY NOTATION	

17 COSATI CODES		
FIELD	GROUP	SUB-GROUP

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)

19 ABSTRACT (Continue on reverse if necessary and identify by block number)

DTIC ELECTE AUG 10 1989 S E D

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT ☐ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION
22a. NAME OF RESPONSIBLE INDIVIDUAL Gloria Ruggiero	22b. TELEPHONE (Include Area Code) (202) 295-2017
	22c. OFFICE SYMBOL ISDP

DD FORM 1473, 84 MAR — 83 APR edition may be used until exhausted. All other editions are obsolete.

SECURITY CLASSIFICATION OF THIS PAGE
UNCLASSIFIED

89 8 08 147

UNCLASSIFIED
SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION UNCLASSIFIED	1b RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT DISTRIBUTION UNLIMITED
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) FJSRL-JR-87-0010	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION Frank J. Seiler Research Lab 6b. OFFICE SYMBOL (If applicable) FJSRL/NC	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code) USAF Academy Colorado 80840-6528	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION AF Office of Scientific Research 8b. OFFICE SYMBOL (If applicable) AFOSR	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code) Bldg 410 Bolling AFB, DC 20332	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 61102F; PROJECT NO. 2303; TASK NO. F3; WORK UNIT ACCESSION NO. 07

11. TITLE (Include Security Classification)
MNDO Cluster Model Calculations on Organic Polymers

12. PERSONAL AUTHOR(S)
J.J.P. Stewart

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Journal Article	FROM _____ TO _____	87/02/06	9

16. SUPPLEMENTARY NOTATION

17. COSATI CODES		
FIELD	GROUP	SUB-GROUP

18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
MNDO, heat of polymerization, clusters, polymers, heat of formation

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

Heats of formation and unit cell translation vectors for several organic polymers are calculated using the NMDO method. The results compare favorably with experiment; the magnitude of the errors is comparable to those of the NMDO method when applied to molecules.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT ☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	21. ABSTRACT SECURITY CLASSIFICATION UNCLASSIFIED
22a. NAME OF RESPONSIBLE INDIVIDUAL J.J.P. STEWART	22b. TELEPHONE (Include Area Code) (719)472-2655 22c. OFFICE SYMBOL FJSRL/NC

DD Form 1473, JUN 86 *Previous editions are obsolete.*

SECURITY CLASSIFICATION OF THIS PAGE
UNCLASSIFIED

RADIATION RESEARCH 117, 419–432 (1989)

Gamma Radiation Affects Active Electrolyte Transport by Rabbit Ileum

II. Correlation of Alanine and Theophylline Response with Morphology

PAMELA J. GUNTER-SMITH

Physiology Department, Armed Forces Radiobiology Research Institute, Bethesda, Maryland 20814-5145

GUNTER-SMITH, P. J. Gamma Radiation Affects Active Electrolyte Transport by Rabbit Ileum. II. Correlation of Alanine and Theophylline Response with Morphology. *Radiat. Res.* **117**, 419–432 (1989).

The response of ileal segments isolated from rabbits to an actively transported amino acid and a secretagogue was evaluated following exposure to 10 Gy whole-body γ irradiation. The ability of ileal segments to respond to the actively transported amino acid, alanine, was not significantly diminished until 96 h postexposure. Decreased responsiveness to the secretagogue, theophylline, occurred earlier at 72 h. These effects did not appear to be accounted for by decreased food intake of irradiated animals alone. Examination of intestinal morphological changes with respect to these changes in electrolyte transport revealed that decreased amino acid transport coincides with loss of intestinal villi. Although a morphological correlate of decreased secretory response was not as striking as that for absorption, the theophylline response appeared to decline concomitant with the appearance of increased mitotic activity in the intestinal crypts. The results of this study indicate that, following a dose of 10 Gy, the inability of these tissues to respond to amino acids is due to a loss of mature villus absorptive cells subsequent to denudation of the intestinal mucosa. There appeared to be little impairment of cell membrane transport processes for alanine. In contrast, the decreased secretory response could not be correlated with the disappearance of any one cell type and perhaps results from increased proliferation in the crypts at the expense of differentiation.

INTRODUCTION

Although effects of ionizing radiation on the gastrointestinal tract have been well documented (reviewed in (*1, 2*)), recent studies continue to provide new insight into the mechanisms underlying postirradiation dysfunction. Many studies have focused on the effects of radiation on nutrient absorption (*3–8*). There is, however, essentially little information concerning the effect of radiation on the other mode of transport in these tissues, electrolyte secretion. Not only are cellular transport processes underlying secretion different from those associated with absorption, absorptive and secretory cells appear to be localized to distinct regions of the intestinal mucosa, villus and crypt, respectively (*9–11*). Recent observations from this laboratory (*12*) indicated that active transcellular electrolyte secretion is stimulated 24 h following radiation exposure, which may contribute to fluid and electrolyte loss. Thus information con-

0033-7587/89 $3.00

cerning the effect of radiation on secretory as well as absorptive processes is important to an understanding of intestinal dysfunction postirradiation.

To examine the role of membrane transport processes in postirradiation intestinal dysfunction in greater detail, this study assesses in rabbit ileum the effect of radiation on two well-characterized active transport processes. Both absorption, stimulated by amino acids, and secretion, stimulated by theophylline, are evaluated. These data are correlated with changes in morphology to examine the relation between functional and morphological damage induced by exposure to ionizing radiation. In addition, since absorption and secretion are localized to different areas, the results are discussed with respect to regional effects of radiation. The results show that both absorption and secretion are inhibited by radiation exposure with different time courses. Further, in some cases, this loss of function can be attributed to the demise of a population of intestinal cells.

METHODS

Male New Zealand White rabbits (Hazelton Dutchland, Denver, PA) weighing 2–3 kg were screened for evidence of disease prior to use. They were individually housed in stainless steel cages and maintained in rooms at 21°C, 50% RH, 12 h light/12 h dark (no twilight). They were allowed access to commercial chow and tap water *ad libitum* except for "fasted" animals from which food was withheld. All procedures used for animal irradiation and assessment of transepithelial transport have been reported previously (*12*). Briefly, the terminal ileum was isolated from euthanatized New Zealand White rabbits (80 mg/kg iv. pentobarbital sodium) that were either exposed to 10 Gy whole-body ^{60}Co radiation, sham irradiated, or fasted. These tissues are referred to as irradiated, control, and fasted, respectively. The following times were selected for isolation of tissues from the animal: 24, 48, 72, or 96 h postirradiation or postfast.

For the assessment of transepithelial electrical parameters, the tissues were mounted in chambers and bathed with a standard Ringer's solution (*12*). Transepithelial potential (PD), resistance (R_t), and short-circuit current (I_{sc}, which represents the sum of all active transcellular ion movements across the tissue) were monitored as previously described (*12*). After steady-state baseline values were achieved (generally 80–100 min), the response of the intestinal segments to an actively transported amino acid was determined by the addition of alanine from stock solutions to the luminal bath (final concentration, 10 m*M*). Subsequently, alanine was removed allowing the reestablishment of baseline values and then replaced by Ringer's containing the secretagogue theophylline (10 m*M*). The response of irradiated and fasted segments was always compared to that of a control animal from the same "batch" of animals to minimize differences arising from different groups of animals. All results are expressed as the mean ± SEM. Significant differences from control were determined at the 0.05 level using the Student's *t* test.

Additional segments of tissue isolated from the same animals used in transport studies were prepared for morphological examination. Sections were stained with hematoxylin and eosin and examined for qualitative changes in morphology postirradiation.

RESULTS

Transport studies. The results of a typical experiment are shown in Fig. 1 in which the response of ileal segments isolated from an irradiated animal 24 h postexposure is compared to that from a control animal. Although the baseline I_{sc} was elevated 24 h postirradiation, the response of the tissue to both alanine and theophylline was essentially identical to control. Previous studies from this laboratory (*12*) have shown that the elevated basal I_{sc} postirradiation reflects a stimulation of cellular secretory processes (blood to lumen) that are similar to those elicited by secretagogues such as theophylline (*13*). This differs from the ionic basis of the increase in I_{sc} following alanine addition, which reflects increased transcellular absorptive processes (*9*).

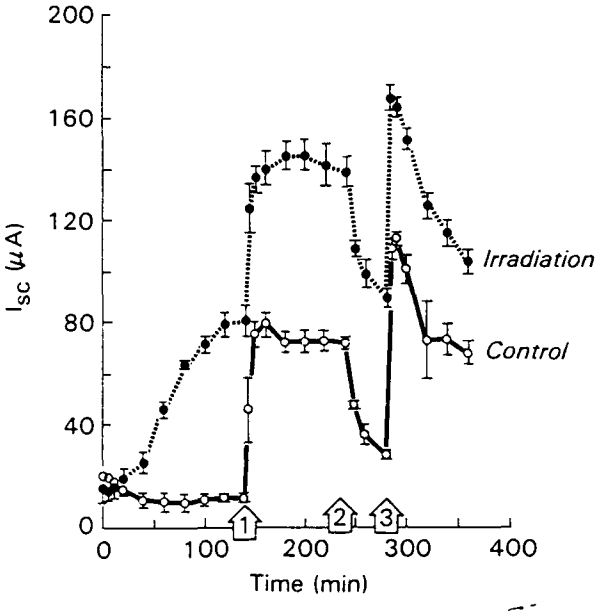

FIG. 1. I_{sc} of ileal segments from a control and an irradiated animal (10 Gy) with respect to time after mounting in chambers. Each point is the mean of values for four segments from the same animal. Arrows labeled 1, 2, and 3 indicate alanine addition, alanine removal, and theophylline addition, respectively.

The time course of differences in the response of irradiated segments (10 Gy) to alanine or theophylline with respect to controls is shown in Fig. 2. There were no significant differences observed in the response to alanine until 96 h postexposure by which time the response was greatly diminished. Significant declines in the response of irradiated segments to theophylline were observed to occur earlier at 72 h postirradiation.

Since food intake of irradiated animals initially decreases following exposure, the effect of fasting on the response to alanine and theophylline was evaluated in control

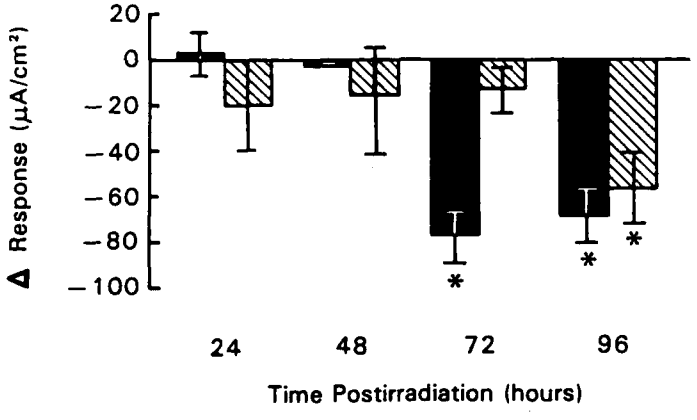

FIG. 2. Response of irradiated tissues to alanine (hatched bars) and theophylline (filled bars) compared to controls with respect to time postirradiation. ΔResponse = ΔI_{sc} (irradiated) − ΔI_{sc} (control); n = 4 irradiated and 4 control tissues for each bar; * indicates significant difference.

TABLE I

The Effect of Fasting on the Response to Alanine and Theophylline

	24 h	*48 h*	*72 h*	*96 h*
Alanine	6.6 ± 15.4	−54.8 ± 11.3	−17.7 ± 12.5	−22.3 ± 11.9
P	NS	<0.03	NS	NS
Theophylline	11.2 ± 14.4	−28.0 ± 5.7	−42.9 ± 20.6	−44.8 ± 26.2
P	NS	<0.03	NS	NS

Note. Data are expressed as the mean of ΔI_{sc} (fasted) − ΔI_{sc} (control) for four experiments. NS = nonsignificant.

animals. As shown in Table I, the response of "fasted" animals to both alanine and theophylline was decreased compared to nonfasted controls at 48 h postfast. Differences in the response were not significant at the other times studied including those at which significant effects of radiation were noted. Direct comparison of the fasting with the irradiated data (Table I and Fig. 2), however, did not show significant differences between these two groups at 72 or 96 h.

Morphology. The morphology of ileal segments isolated from tissues used in the transport studies above was examined in an attempt to further define the factors underlying the changes in transport properties following radiation exposure. Figure 3 shows the typical appearance of an ileal segment from a control animal. Long finger-like projections, villi, protrude into the lumen with numerous crypts at their base (Fig. 3A). Cells lining the villi are columnar epithelial cells; their brush borders (composed of microvilli on the individual cells) are clearly visible in Fig. 3B. A smaller population of mucus-secreting goblet cells is also present. In contrast to the villus area, the crypt area (shown in Fig. 3C) has at least five main cell types (*14*). Three of these are easily identified in the field: Paneth cells located at the base of the crypt, goblet cells, and a proliferative cell in which a mitotic figure is visible. Argentaffine and undifferentiated crypt cells are not easily identified in this section.

The effects of radiation on the morphology of rabbit ileum was similar to that observed in this and other species for a dose that is considered "threshold" for gut injury (*15*). The severity of the damage was quantitatively less than that associated with pure gut death and a proliferative burst was observed in the crypts at the later times. The time course of the changes in morphology is detailed in Figs. 4–7. At 24 h postexposure little change in the gross morphology of the tissue is visible (Fig. 4A). There is no obvious blunting of the villi and the brush border membranes are still prevalent (Fig. 4B). There is no major disruption of the crypt epithelium, although discrete areas of cell death are visible (Fig. 4C). While the radiosensitive cells cannot be identified in the figure, the Paneth cell population appears virtually unaffected. Interestingly, mitotic figures are not frequently seen at this time, suggesting that, while major alterations in morphology have not occurred, mitosis has been interrupted. Blunting of the villi is observed by 48 h postirradiation, and a greater proportion of the villus appears occupied by goblet cells compared to control (Figs. 5A, 5B). Cell death in the crypts appears comparable to that at 24 h. However, at this time mitotic

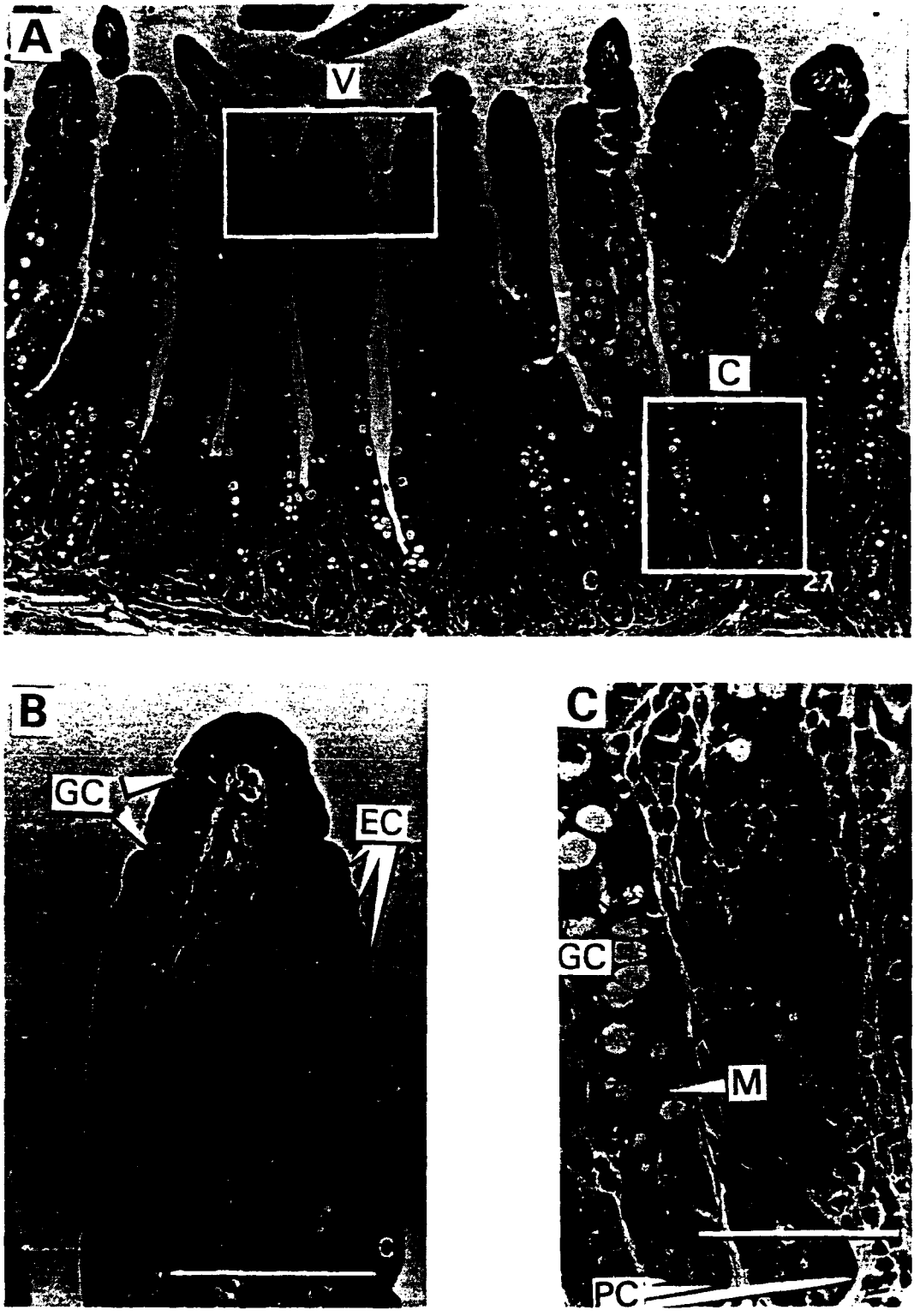

FIG. 3. (A) Morphology of ileal segment from a control animal. Villus (V) and crypt (C) regions are designated. Boxes indicate regions from which higher magnifications ((B) and (C)) were taken. (B) Higher magnification of villus showing goblet (GC) and epithelial cells (EC). (C) Higher magnification of crypt showing goblet (GC) and Paneth cells (PC). A mitotic figure is shown at M. The scale shown is 200 μm.

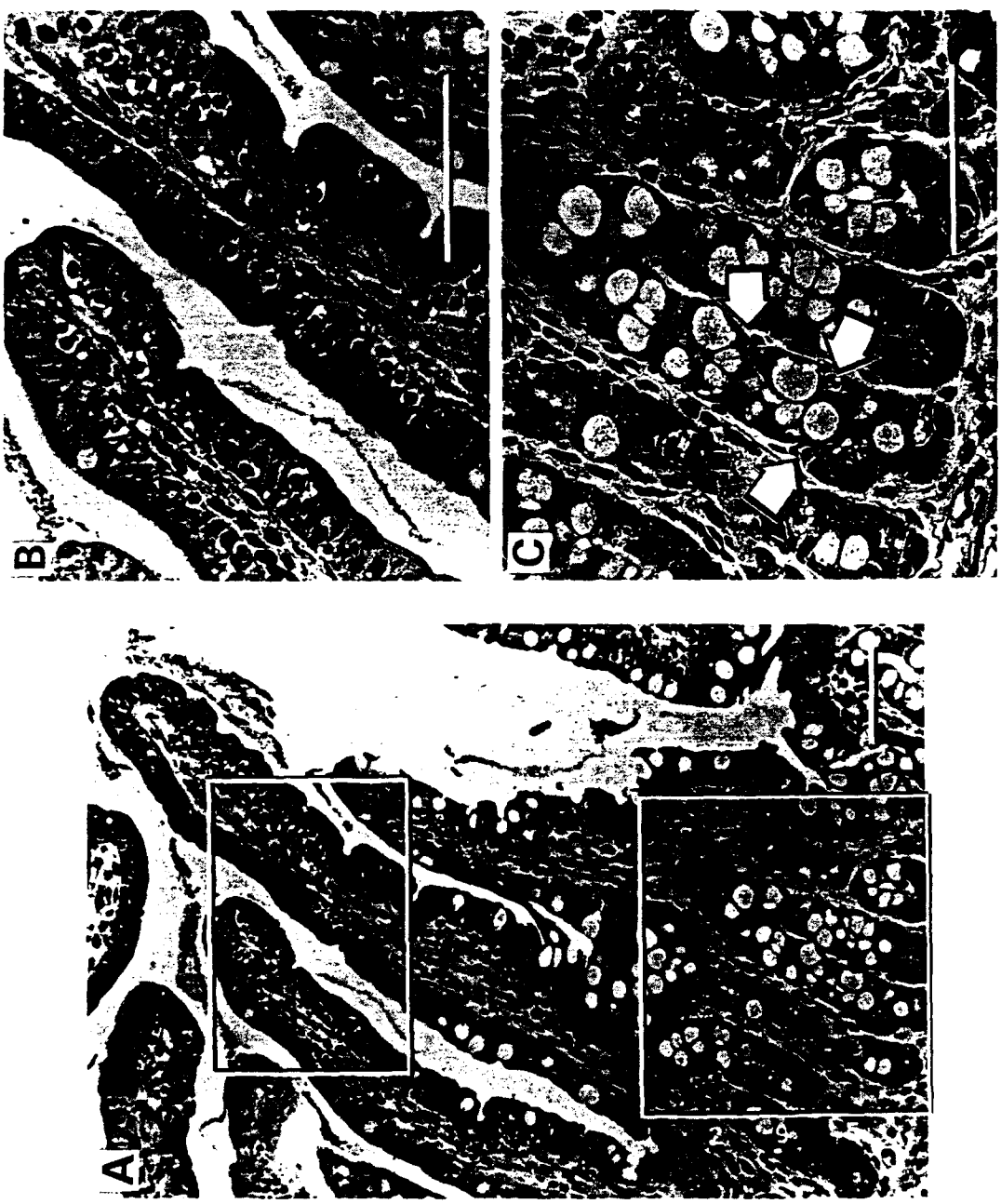

FIG. 4. (A) Gross morphology of ileal segment 24 h postirradiation. Higher magnification of villus and crypt regions is shown in (B) and (C), respectively. Arrows indicate cell damage. Scale shown is 200 μm.

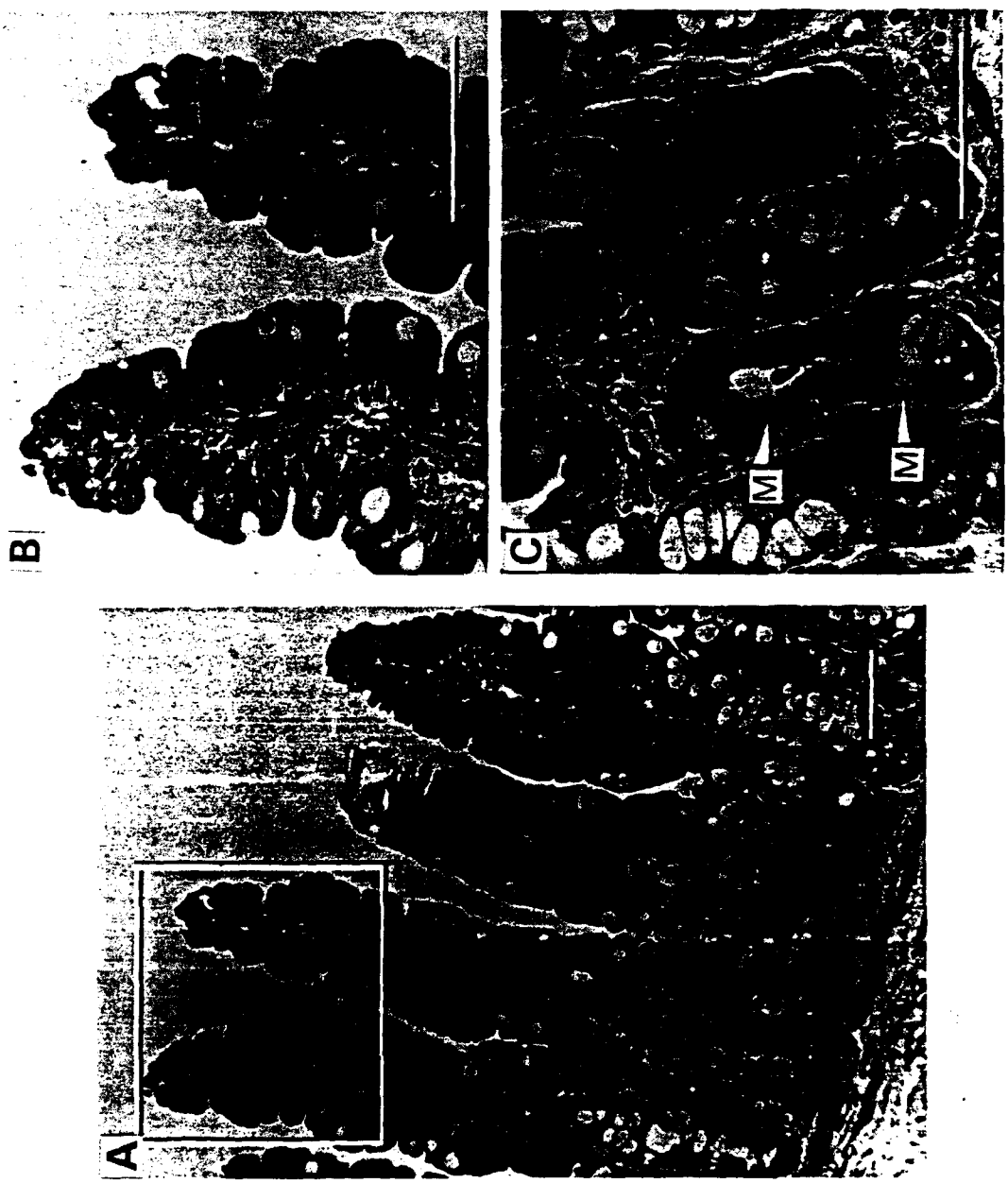

FIG. 5. (A) Gross morphology of ileal segment 48 h postirradiation. Higher magnification of villus region shown in (B) is from boxed area of (A). Higher magnification of the crypt regions shown in (C) is from a different area of the same section. M designates mitotic figures. Scale is 200 μm.

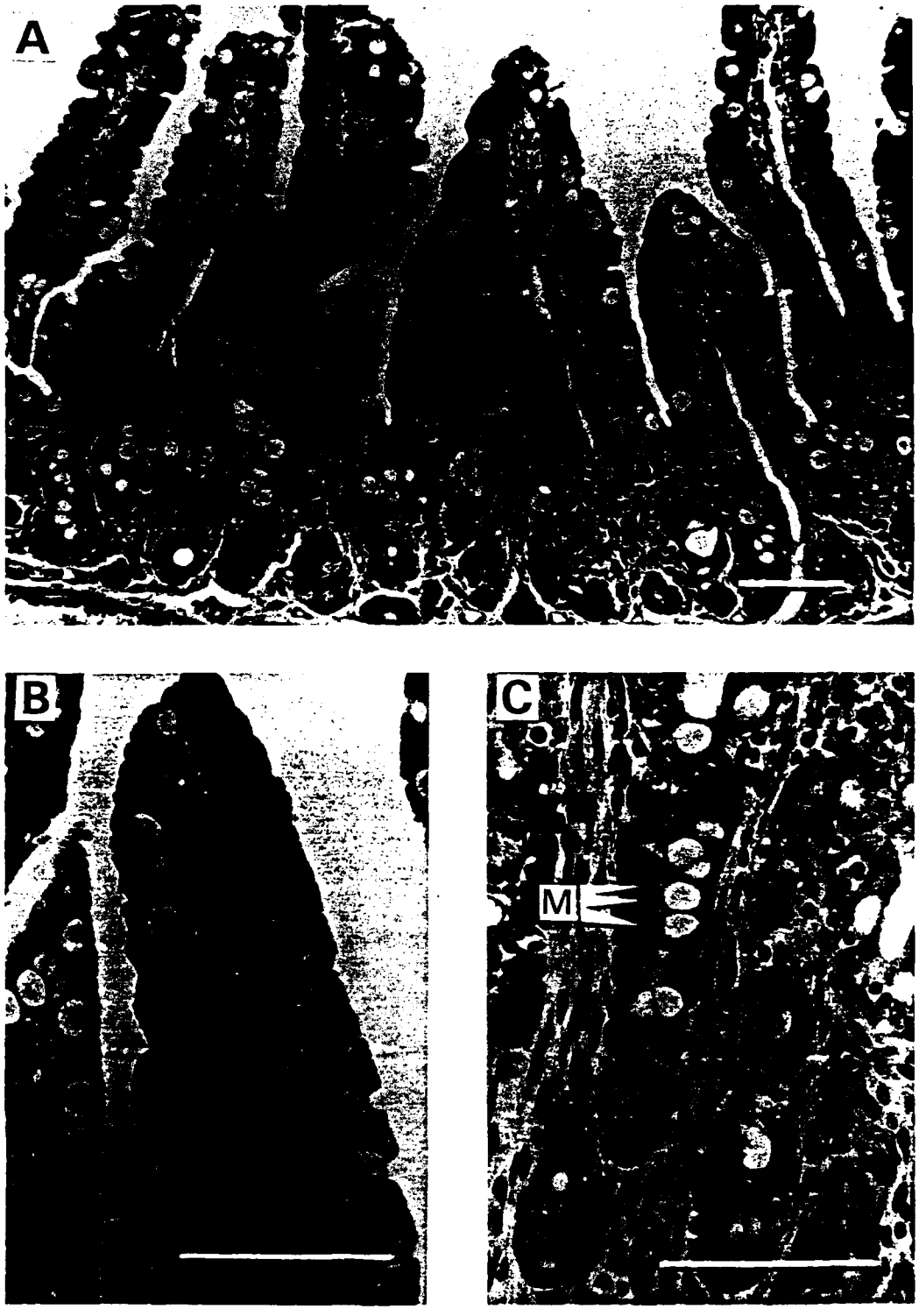

FIG. 6. (A) Gross morphology of ileal segment 72 h postirradiation. Higher magnification of villus and crypt regions in (B) and (C) is taken from different sections but from the same animal. A mitotic figure is shown at M. Scale is 200 μm.

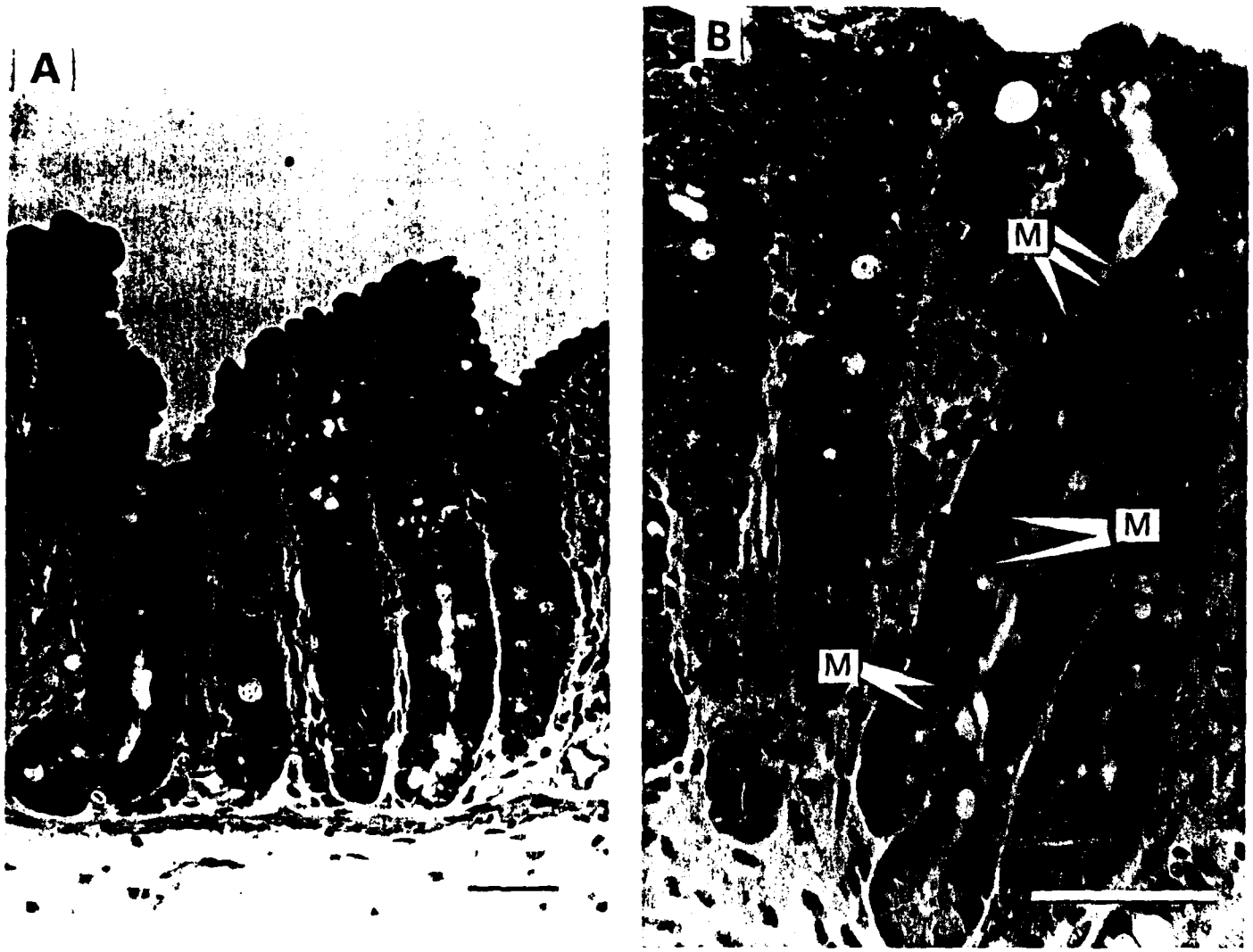

FIG. 7. Intestinal morphology 96 h postirradiation. Higher magnification of crypt epithelium shown in (B) is from a different section from the same animal. M designates mitotic figures. Scale is 200 μm.

figures are observed once again (Fig. 5C). Similar changes in morphology are observed 72 h postirradiation (Figs. 6A, 6B); blunting of the villi appears to have increased. The number of mitotic figures appearing in the crypt area also seems to have increased in Fig. 6C. By 96 h postirradiation, blunting of villi has progressed until they are virtually absent (Fig. 7A). Where not denuded, the villus remnants are covered with cuboidal rather than columnar cells (Fig. 7B). The overall depth of the crypt epithelium has increased. Mitotic figures are numerous and observed even in the neck region of the crypt. This was not seen at earlier times. Thus the entire mucosa appears to be undergoing a proliferative burst at this time, perhaps in an attempt to repopulate the mucosa with viable cells.

DISCUSSION

In an earlier study (*12*), changes in basal transcellular electrolyte transport processes of rabbit ileum were described with respect to dose and time after radiation exposure. The results indicated that a stimulation of electrolyte secretory processes occurred 18–24 h postirradiation that was suggested to contribute to fluid and electrolyte loss associated with the gastrointestinal syndrome. In the present study, changes in the physiological function of the intestinal mucosa with radiation have been explored in greater detail and correlated with morphological changes. The response of ileal segments from irradiated animals was determined for both an actively transported amino acid, alanine, and a secretagogue, theophylline. Since the responses of the tissue to these agents have been previously attributed to different cell populations (*9–11*), evaluation of these processes allows differential examination of functional damage to these two regions of the intestinal mucosa.

Increases in I_{sc} following the addition of actively transported amino acids and sugars to the luminal solution have previously been shown to reflect increased transcellular Na absorption (*9*). Na absorption is stimulated because the influx of sugars and amino acids into the cell is energetically coupled to Na entry. In addition, overall fluid absorption is increased in the process due to the resulting osmotic driving force. Previous studies have provided compelling evidence that only the columnar epithelial cells lining the intestinal villi acquire transport processes required to absorb sugar and amino acids at some time during migration along the villus (*16*). Thus the assessment of the response to alanine following radiation exposure specifically probes one facet of the functional integrity of the villus epithelium.

A significant effect of radiation on the response of ileal segments to alanine was not observed until 96 h postexposure by which time the response was virtually absent. Morphological examination of the tissue indicated that this decline in the response to alanine coincided with the disappearance of the intestinal villi. Since the electrical resistance of the tissue was previously shown to be maintained at this time (*12*), the I_{sc} still appears to assess transport accurately in these tissues. Thus decreased amino acid transport can be attributed to a loss of absorptive villus cells, rather than to an effect of radiation on the underlying cellular transport mechanisms.

Previous studies of the effect of radiation on nutrient absorption by rat intestine postirradiation (*3–7*) reported decreased intestinal absorption at 72 h consistent with the results of the present study. In some cases (*3–6*), an initial increase was observed

at 20 h that was not seen in the present study. Reduced nutrient transport postirradiation was attributed to an impairment of underlying cellular transport processes. However, in support of the conclusions drawn in the present study, reduced transport often coincided with severe morphological damage to the intestinal mucosa (*5, 6*). Likewise, Kwock *et al.* (*17*) observed that decreased Na-dependent amino acid transport in lymphoid cells immediately preceded decreased cell viability. Additional support for the notion that decreased nutrient transport does not result from impaired cellular transport processes is found in more recent studies in which the effects of radiation on transport can be clearly distinguished from cell killing and effects on proliferation. Cheeseman *et al.* (*8*) observed no change in leucine transport in enterocytes isolated from rats 3 days after 6 Gy; glucose transport was actually enhanced in these cells. This latter effect was suggested to be compensatory subsequent to a loss of absorptive surface area. Additionally, Moran *et al.* (*18*) observed no change in basal Na-coupled sugar transport following irradiation of cultured renal epithelial cells. They observed, however, an inability of irradiated cells (>5 Gy) to up-regulate the number of glucose transporters when given an appropriate stimulus that was attributed to an effect of radiation on gene expression.

In addition to studying nutrient absorption, this study also examines intestinal secretory processes postirradiation. Assuming (as is generally accepted) that these processes reside in cells of the crypt epithelium (*9–11*), evaluation of the response of the tissue to a secretagogue such as theophylline will assess the functional integrity (in terms of transport) of this region. Theophylline was observed to increase I_{sc} of control as well as irradiated intestinal segments at early times postexposure (<72 h). The increase in I_{sc} elicited by theophylline is related to a stimulation of anion secretory processes (*13*). As is true for osmotic fluid absorption resulting from alanine transport, this secretory process stimulates the secretion of fluid into the intestinal lumen. Indeed, it is the stimulation of cellular secretory processes that is responsible for fluid and electrolyte loss associated with a large number of diarrheal diseases (*19*).

Decreased responsiveness of ileal segments to secretagogues was observed 72 h postirradiation. Examination of the morphology of the intestinal mucosa at this time revealed blunting of the villi and increased mitotic activity in the crypts. By 96 h postirradiation, mitotic figures were observed even at the neck of the crypts, but a major loss of cellularity in the crypt epithelium during this time was not apparent. Thus, as described previously for the small intestine of other species (*20–22*), rabbit ileum apparently undergoes a proliferative burst in an attempt to repopulate the intestinal mucosa. Evaluation of transport data with respect to the morphology of the crypt epithelium would suggest that, in contrast to absorption, secretion is diminished in spite of a maintenance of cellularity in the crypt epithelium. Since substantial blunting of the villi does occur 72 h postirradiation, this result could be interpreted as indicating that some villus cell population that is secretory is lost by this time. Since amino acid transport (clearly a villus cell function) was not diminished at 72 h but was diminished at 96 h, this would require a preferential decline in secretory processes and/or enhancement of absorptive processes in these cells. Given the evidence suggesting that secretion is localized to the crypts (cf. (*9–11*)) and that increased mitosis is observed at 72 h, a more attractive explanation for the data is that the

inability of the tissue to respond to a secretagogue is related to decreased differentiation of the crypt cell population.

These results complement our earlier observations (*12*) of changes in basal active electrolyte transport postirradiation. A secretory response was observed which peaked between 18 and 24 h postirradiation and subsequently declined. The basis of this time course was unexplained. It now appears reasonable to suggest that as for secretion stimulated *in vitro* by theophylline, the basal secretory response postirradiation declines due to population of the intestinal crypts with less differentiated cells undergoing mitosis.

In interpreting the results of this study with respect to the effect of radiation on intestinal function, two important caveats require consideration. The first is that the experimental conditions employed may not precisely reflect the environment of the irradiated intestine *in vivo*. This is a consequence of the requirements for measuring active transcellular intestinal transport which must be done *in vitro* using a well-defined media bathing the tissue. Thus the tissue is not exposed to various substances normally present in the lumen (e.g., bile and pancreatic enzymes) or blood that may contribute to alterations in intestinal transport postirradiation. This concern is tempered, however, by the fact that the tissues used in this study were isolated from the animal immediately before transport was assessed and therefore exposed to these *in vivo* factors from the time of exposure to the time of measurement. Prolonged effects and/or damage from such agents would still be observed in these studies, and although short-lived effects would not be observed, they are less likely to be factors in the response.

The second caveat is that the changes observed may not reflect direct radiation damage to the intestinal mucosa, but secondary effects of agents such as those discussed above or other factors resulting from radiation exposure. One of these is the possible influence of decreased food intake observed in irradiated animals which was evaluated in this study by comparing the response of fasted animals to alanine and theophylline to that of their matched controls in a separate series of experiments. Diminished alanine and theophylline responses of segments from fasted animals were significant at 48 h but not at later times when significant effects were observed between irradiated animals and controls. Although the magnitude of the differences in the response for irradiated animals was nearly twice that of fasted animals, a direct comparison of the data from these two groups did not reveal statistically significant differences between fasting and irradiation at 72 or 96 h. While this may be related to the degree of variance associated with the physiological response of the two groups to these conditions, it prevents concluding unequivocally that decreased food intake is not a factor in the radiation response. However, considering that irradiated animals are not totally fasted and have resumed eating by 72 h postexposure, the direct comparison of fasting and irradiated data may overestimate the role of fasting in the response of irradiated tissues. This taken together with previous studies of starving rats (*23, 24*) indicating less severe morphological changes than those observed in this study in irradiated rabbits makes it difficult to reconcile the results from irradiated animals as only secondary to decreased food intake.

In summary, the response of the intestinal mucosa to an actively transported amino acid and a secretagogue was used to assess differential effects of radiation on

villus and crypt epithelia, respectively. These results taken together with the morphological changes observed suggest that secretory processes decline at 72 h perhaps due to increased proliferation in the crypts at the expense of differentiation. Nutrient absorption was observed to decline later at 96 h and was related to the loss of mature villus cells which normally occupy the intestinal villus.

ACKNOWLEDGMENTS

The author thanks L. Heman-Ackah for preparation of tissues for light microscopy; T. Wilczynski for technical assistance in transport studies; and Dr. J. Nold for helpful discussions concerning the morphological studies. This work was supported by the Armed Forces Radiobiology Research Institute, Defense Nuclear Agency, under research work unit MJ00107. The views presented in this paper are those of the author: no endorsement by the Defense Nuclear Agency has been given or should be inferred. Research was conducted according to the principles enunciated in the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council.

RECEIVED: February 9, 1988; REVISED: September 15, 1988

REFERENCES

1. V. P. BOND, T. M. FLIEDNER, and J. O. ARCHAMBEAU, *Mammalian Radiation Lethality.* Academic Press, New York, 1965.
2. P. J. GUNTER-SMITH, Effect of ionizing radiation on gastrointestinal physiology. In *Military Radiobiology* (J. J. Conklin and R. I. Walker, Eds.), pp. 135–151. Academic Press, Orlando, FL, 1987.
3. M. F. SULLIVAN, Absorption of the gastro-intestinal tract of the rat after X-irradiation. *Am. J. Physiol.* **201,** 1013–1017 (1961).
4. A. D. PERRIS, Intestinal transport and metabolism following whole-body irradiation. *Radiat. Res.* **29,** 597–602 (1968).
5. A. BECCIOLINI, G. B. GERBER, and J. DEROO, In vivo absorption of carbohydrates in rats with gastrointestinal radiation syndrome. *Acta Radiol. Ther. Phys. Biol.* **16,** 87–96 (1977).
6. M. MOHUIDDIN, K. TAMURA, and P. DEMARE, Changes in absorption of glucose and proline following irradiation to the exteriorized ileum. *Radiat. Res.* **74,** 186–190 (1975).
7. A. B. R. THOMSON, C. I. CHESSEMAN, and K. WALKER, Effect of abdominal irradiation on the kinetic parameters of intestinal uptake of glucose, galactose, leucine, and gly-leucine in the rat. *J. Lab. Clin. Med.* **102,** 813–827 (1983).
8. C. L. CHEESEMAN, A. B. R. THOMSON, and K. WALKER, The effects of abdominal irradiation on intestinal transport in the rat as assessed with isolated epithelial cells. *Radiat. Res.* **101,** 131–143 (1985).
9. S. G. SCHULTZ, R. A. FRIZZELL, and H. N. NELLANS, Ion transport by mammalian small intestine. *Annu. Rev. Physiol.* **36,** 51–91 (1974).
10. M. FIELD, Intracellular mediators of secretion in the small intestine. In *Mechanisms of Intestinal Secretion* (H. J. Binder, Ed.), pp. 83–91. Alan R. Liss, New York, 1979.
11. R. A. FRIZZELL and S. G. SCHULTZ, Models of electrolyte absorption and secretion by gastrointestinal epithelia. In *International Review of Physiology (Gastrointestinal Physiology III)* (R. K. Crane, Ed.), Vol. 19, pp. 205–225. Univ. Park Press, Baltimore, 1979.
12. P. J. GUNTER-SMITH, Ionizing radiation affects active electrolyte transport by rabbit ileum: Basal Na and Cl transport. *Am. J. Physiol.* **250** (*Gastrointest. Liver Physiol.* 13), G540–G545 (1986).
13. M. FIELD, Ion transport in rabbit ileal mucosa. II. Effects of cyclic 3',5"-AMP. *Am. J. Physiol.* **221,** 992–997 (1971).
14. J. S. TRIER, Morphology of the epithelium of the small intestine. In *Handbook of Physiology.* (C. F. Code, Ed.), Sect. 6, Vol. III, pp. 1125–1175. Am. Physiol. Soc., Washington, 1968.
15. J. MAISIN, J. R. MAISIN, and A. DUNJIC, The gastrointestinal tract. In *Pathology of Irradiation.* (C. C. Berdjis, Ed.), pp. 296–344. Williams & Wilkins, Baltimore, 1971.

16. W. B. KINTER and T. H. WILSON, Autoradiographic study of sugar and amino acid absorption by everted sacs of hamster intestine. *J. Cell Biol.* **25,** 19–39 (1965).
17. L. KWOCK, P.-S. LIN, and L. CIBOROWSKI, Differences in the effect of ionizing radiation on Na^+-dependent amino acid transport in Human T (Molt-4) and Human B (RPMI 1788) Lymphoid cells. *Radiat. Res.* **80,** 512–533 (1979).
18. A. MORAN, L. DAVIS, and M. HAGAN, Effect of radiation on the regulation of sodium-dependent glucose transport in LLC-PK_1 epithelial cell line: Possible model for gene expression. *Radiat. Res.* **105,** 201–210 (1986).
19. H. J. BINDER. Net fluid and electrolyte secretion. In *Mechanisms of Intestinal Secretion* (H. J. Binder, Ed.), pp. 1–16. Alan R. Liss, New York, 1979.
20. S. LESHER and J. BAUMAN, Recovery of reproductive activity and the maintenance of structural integrity of the intestinal epithelium of the mouse after single dose whole-body 60-Co gamma ray exposure. In *Effect of Radiation on Cellular Proliferation and Differentiation. Proceedings of a Symposium on the Effects of Radiation on Cellular Proliferation and Differentiation,* pp. 507–513. IAEA, Vienna, 1968.
21. H. C. YAU and A. B. CAIRNIE, Cell-survival characteristics of intestinal stem cells and crypts of Co-irradiated mice. *Radiat. Res.* **80,** 92–107 (1979).
22. W. R. HANSON, D. L. HENNINGER, R. J. M. FRY, and A. R. SALLESE, The response of small intestinal stem cell in the mouse to drugs and irradiation treatment. In *Cell Proliferation of the Gastrointestinal Tract* (D. R. Appleton, J. P. Sunter, and A. J. Watson, Eds.), pp. 198–212. Pitman Medical, Marshfield, 1980.
23. M. STEINER, H. R. BOURGES, L. S. FREEDMAN, and S. J. GRAY, Effect of starvation on the tissue composition of the small intestine in the rat. *Am. J. Physiol.* **215,** 75–77 (1968).
24. E. S. DEBNAM and R. J. LEVIN, Effect of semistarvation on the kinetics of active and passive sugar absorption across the small intestine in vivo. *J. Physiol.* **252,** 681–700 (1975).